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ScienceDirect
Animal Feed Science and Technology
137 (2007) 201–212

ANIMAL FEED SCIENCE AND TECHNOLOGY

www.elsevier.com/locate/anifeedsci

Review

An historical overview of field disease outbreaks known or suspected to be caused by consumption of feeds contaminated with *Fusarium* toxins

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Abstract

The interest in mycotoxins began when aflatoxins were found to be carcinogens and to be widespread in foodstuffs and feedstuffs. Today, mycotoxins and mouldy feedstuffs are known causes of animal disease. Symptoms are often subtle and there can be many equally non-definitive contributing factors; for example, environmental stress, exposure to multiple mycotoxins and infectious agents, and nutrient/vitamin deficiencies. Thus, it is often difficult to establish cause–effect relationships with contaminated feedstuffs. The *Fusarium* toxins of greatest concern are deoxynivalenol (DON), fumonisins, and zearalenone. For each, mould-contaminated feed was implicated as the cause of animal disease long before the toxins were identified. In the field, changes in performance or behaviour and increased susceptibility to infectious disease are possible subtle signs of exposure to mycotoxins in feed. Because most cases of toxicity present non-specific clinical signs, cases of suspected mycotoxicosis often remain unreported. Nonetheless, for DON, fumonisin and zearalenone there are signs that are highly suggestive of exposure. For DON a commonly observed effect is feed refusal which has been reported in cattle, pigs and chickens; however, pigs appear to be the most sensitive. Although DON is not considered to be acutely toxic to farm animals, it is considered to be a major cause of economic loss due to reduced performance. In pigs, the reduction in feed intake occurs relatively soon after consuming feeds containing greater than 1 mg deoxynivalenol/kg and emesis at >10 mg/kg. Field outbreaks of mouldy maize-induced equine leukoencephalomalacia (ELEM) have been reported

Abbreviations: ELEM, equine leucoencephalomalacia; PPE, porcine pulmonary edema; DON, deoxynivalenol

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0377-8401/$ – see front matter. Published by Elsevier B.V.
doi:10.1016/j.anifeedsci.2007.06.002

since 1891 and in 1988 pure fumonisin was shown to produce ELEM in a horse. ELEM syndrome is a fatal disease that apparently occurs only in equids. The length of exposure, level of contamination, individual animal differences, previous exposure, or pre-existing liver impairment may all contribute to the appearance of the clinical disease. Analysis of feeds from confirmed cases of ELEM indicates fumonisin B_1 concentration greater than 10 mg/kg in the diet is associated with increased risk of ELEM. Another disease caused by fumonisin is porcine pulmonary edema syndrome. Zearalenone has been implicated in field outbreaks of reproductive problems, vulvovaginitis and anestrus in pigs. The primary effect of zearalenone is estrogenic and prepubertal female pigs are the most affected animal. The history of discovery of mycotoxin involvement in animal diseases serves as a warning that yet to be discovered mycotoxins could also be involved in current or future inexplicable animal production problems.
Published by Elsevier B.V.

Keywords: Mycotoxins; *Fusarium* toxins; Deoxynivalenol; Fumonisin; Zearalenone

Contents

1. Introduction

Even before the discovery of aflatoxins, the occurrence of large increases in the incidence of acute diseases, not associated with known infectious diseases and often involving mortality or evidence of acute toxicity, in farm animals signaled the presence of mycotoxins in feeds (Forgacs and Carll, 1962). Nonetheless, the current interest of the scientific and regulatory communities in mycotoxins began in earnest when aflatoxins were shown to be potent carcinogens and to be widespread in foodstuffs and feedstuffs. Today, even though there is a great deal of experimental evidence characterizing the potential of mycotoxins and mouldy feedstuffs to cause animal disease, definitively linking a disease outbreak in the field to a specific mycotoxin can be very difficult (Hamilton, 1982). Briefly, the problem is that mycotoxins often do not cause acute disease and, when they do, there are often multiple interacting factors that can modify the expression of toxicity. For the vast majority of mycotoxicoses, which are chronic, the signs of disease are generally subtle and unspecific, and hence it is more difficult to establish a cause–effect relationship with (contaminated) feedstuffs. Thus, the manifestations of the mycotoxicosis in the field are often not definitive and there can be many equally non-definitive contributing factors; making diagnosis extremely difficult.

For mycotoxins, demonstrating causality through the application of Koch's postulates requires a bioassay that reproduces the disease using the pure compound; however, reproducing the precise conditions that existed in the field, at the dose levels associated with the field outbreak, is confounded by the presence of the multiple contributing factors (environmental stress, multiple mycotoxins, nutrient/vitamin deficiencies, multiple fungi, infectious agents, *etc*.) that can influence the clinical signs, severity and progression of the disease (CAST, 2003). In addition, mycotoxins in feeds are not evenly distributed (Whitaker et al., 2005), thus reproducing the disease at the same dosages as seen in feed samples collected from field can be difficult. According to Osweiler (2000) 100 to 200 kg or more of suspect feed should be saved for confirmatory studies in experimental animals. If the incidence of the disease in the suspected field outbreak is low, experimental confirmation can require a large number of animals.

2. Field outbreaks – historical

For aflatoxin, ergot, deoxynivalenol, fumonisins, and zearalenone, mould-contaminated feed was implicated as the cause of animal disease in field outbreaks long before the toxins were discovered. The outbreak in the 1960s known as "Turkey 'X' disease" led to the discovery of aflatoxins. Nonetheless, outbreaks of liver cancer in farm-raised rainbow trout fed diets containing cotton seed were documented as far back as 1935 (Butler, 1974) and in cattle in 1953 (Raisbeck et al., 1991). The involvement of ergot in animal disease was probably not reported until the middle ages (Christensen, 1980), whereas the biological activity of ergot was known in China over 5000 years ago (Christensen, 1980). There are several reports of ergotism in domestic animals (mainly cattle) in the USA in the early 19th century implicating ergot as the cause of animal production problems (Hesseltine, 1979). In the 1930s US barley was embargoed by Germany due to the presence of factors that caused feed refusal syndrome (Hamilton, 1982); probably involving deoxynivalenol and other trichothecenes. The causative agent(s) for haemorrahagic syndrome caused by mouldy feed (Forgacs and Carll, 1962) has never been identified but could involve multiple mycotoxins including aflatoxin and ochratoxin (Hamilton, 1982). Equine leucoencephalomalacia, first linked to consumption of mouldy maize in 1891 (Haliburton and Buck, 1986), is now known to be caused by fumonisin. Consumption of *Fusarium verticillioides* maize culture material (Kriek et al., 1981) was the first indication that mouldy maize might cause porcine pulmonary edema (PPE) syndrome. After the discovery of the fumonisins, outbreaks of PPE in the USA were shown to be caused by fumonisin. The association of mouldy feed with estrogenism in pigs has been known since 1928 (McNutt et al., 1928). Unlike the aflatoxins ergot, deoxynivalenol, fumonisins and zearalenone, ochratoxin A was isolated and characterized before it was proven in the late 1970s to cause kidney disease outbreaks in poultry (Hamilton et al., 1977) and pigs (Krogh, 1978).

3. *Fusarium* mycotoxins of economic significance

Even though there are hundreds of mycotoxins described in the literature, the number of known mycotoxins that pose a measurable health risk to farm animals is quite limited.

There are several reasons for the limited number of economically important mycotoxins. First, a basic tenet of toxicology is that "the dose makes the poison". This means that, although animals are exposed every day to mycotoxins, the dose is usually insufficient to make them acutely poisonous. Second, although thousands of publications document poisonous effects of fungal metabolites in laboratory experiments, the levels and routes of exposure do not model the exposure of farm animals to naturally contaminated feeds. The potential for toxicity must not be confused with documented and confirmed toxic effects in field situations. Nonetheless, the knowledge derived from *in vitro* studies and with laboratory animals serve as a warning for the possible contribution of mycotoxins in altering immune function (Bondy and Pestka, 2000), contributing to unexplained animal diseases and performance problems in farm animals (Osweiler, 2000). The toxicological effects of *Fusarium* toxins in farm animals are described in detail in other papers included in the special issue (Fink-Gremmels and Malekinejad, 2007; Pestka, 2007; Voss et al., 2007). In addition, there are several excellent reviews that document the toxicology of mycotoxins in animals with extensive descriptions of the clinical manifestations (National Academy of Sciences, 1979; Richard and Thurston, 1986; Raisbeck et al., 1991; JECFA 56th, 2001; CAST, 2003; Haschek et al., 2002; Diaz, 2005; Cousin et al., 2005).

Effects on target organs in farm animals are difficult to detect because mycotoxins typically occur in feeds at low levels. For this reason, changes in animal performance or behavior and increased susceptibility to infectious disease are possible subtle signs of exposure to low levels of mycotoxins in feed. Young animals are more sensitive than adults and nutritional factors such as vitamin or protein-deficient diets can modulate susceptibility as can environmental stress and concurrent exposure to infectious agents and other toxins. Much of what is known about toxicity and target organ specificity is based on laboratory studies in a single species using a single toxin and thus comparative studies are quite rare and dose response relationships comparing domestic animal species and exposure to multiple toxins, as is most likely in field situations, are equally rare.

Mycotoxin-producing *Fusaria* are distributed worldwide and feedstuffs contaminated with their toxins have been found in nearly all published surveys (see Binder et al., 2007; Placinta et al., 1999). In many of the positive samples, the concentration of toxins was high enough to cause overt clinical signs of toxicoses. In spite of the high prevalence of contamination in feeds, the number of described, proven cases of field outbreaks remains low. This can be explained because, as mentioned in previous paragraphs, the manifestation of toxicity is dependent on the dose and length of the exposure. However, for the diagnosis of field outbreaks other factors also contribute to this apparent discrepancy. Under field conditions most cases of toxicosis present non-specific clinical symptoms, well defined symptoms such as those produced by DON intoxication in pigs and fumonisins in horses and pigs are exceptions. In addition, most cases of suspected mycotoxicosis detected by nutritionists and veterinarians remain unreported and the etiological agent responsible for the observed signs is not confirmed when health and production problems improve or disappears following removal of the suspected diets.

It is often difficult to make the link between suspected mycotoxicoses of livestock and the presence of mycotoxins (Shreeve et al., 1975, Abramson et al., 1997). Obtaining representative samples is a major problem that limits diagnosis (Abramson et al., 1997). Improvements in analytical methods and the identification of new toxic molecules should help to confirm

field outbreaks of toxicoses. An example to illustrate this point is the fumonisins, since their discovery in 1988 (Marasas et al., 1988) several cases of feed-associated diseases in various animal species were attributed to these toxins.

The remainder of the current review will provide some brief examples of the spectrum of documented or strongly suspected field outbreaks, typical toxicological effects and species susceptibility for the *Fusarium* toxins, deoxynivalenol, fumonisin, and zearalenone.

4. Deoxynivalenol

Deoxynivalenol and other trichothecenes (including T-2 toxin and diacetoxyscirpenol) have been implicated in farm animal disease outbreaks in many areas of the world. The most commonly observed effect is feed refusal which has been reported in cattle, pigs and chickens; however, pigs appear to be the most sensitive to deoxynivalenol (Rotter et al., 1996; Haschek et al., 2002); the most frequently detected trichothecene in animal feeds. Deoxynivalenol was first isolated in Japan and named "Rd-toxin" (Moorooka et al., 1972). Shortly thereafter, the same compound was isolated from maize associated with emesis in pigs and given the name vomitoxin (Vesonder et al., 1973). Since then there have been many confirmed cases of deoxynivalenol involvement in feed refusal or reduced feed intake in pigs (Osweiler, 2000). Because the primary effect of deoxynivalenol in farm animals is feed refusal, toxic effects are to a great extent self-limiting (Osweiler, 2000). Pet foods are often contaminated with deoxynivalenol and have been suspected to cause feed refusal and other effects in dogs, cats and rabbits; however, to date there are no confirmed field cases found in the accessible literature (Bohm and Razzazi-Fazeli, 2005). Proven field outbreaks of natural intoxication of ruminants with deoxynivalenol are rare (Raisbeck et al., 1991).

Although deoxynivalenol is not considered to be acutely toxic to farm animals, it is considered to be a major cause of economic losses due to reduced performance. In the field, concentrations as low as 1 mg/kg have been associated with feed refusal in pigs, however, more typically, concentrations >2–5 mg/kg are required for decreased feed intake and reduced weight gain and >20 mg/kg for vomiting and feed refusal (Haschek et al., 2002; Trenholm et al., 1988). Clinical signs include gastrointestinal problems, soft stools, diarrhea, increased susceptibility to other diseases and decreased performance. In pigs, mild renal nephrosis, reduced thyroid size, gastric mucosal hyperplasia, increased albumin/alpha-globulin ratio, and sometimes mild changes in other haematological parameters have been reported (JECFA 56th, 2001). Numerous studies in laboratory animals demonstrate alterations in immune function induced by deoxynivalenol (Bondy and Pestka, 2000), but, there is little conclusive evidence that deoxynivalenol induces altered resistance to infectious diseases in the field or in farm animals experimentally (Osweiler, 2000). Nonetheless, the mechanism of action in laboratory animals suggests the potential for involvement in altered immune response in the field.

A urinary biomarker using β-glucuronidase treatment has been developed to estimate the daily intake of deoxynivalenol in people (Meky et al., 2003). This marker may also be useful in suspected field outbreaks in farm animals.

In farm animals the primary target organ for deoxynivalenol toxicity is uncertain. The reason is that the most sensitive effect is reduced weight gain, presumably due to reduced feed

intake and, in pigs, emesis (JECFA 56th, 2001). In pigs, the reduction in feed intake occurs relatively soon after consuming feeds containing greater than 1 mg deoxynivalenol/kg and emesis at >10 mg/kg (Osweiler, 2000; JECFA 56th, 2001). Cattle, sheep, and poultry are resistant to the emetic effects of deoxynivalenol but reduced feed intake was seen at 10–20 mg/kg with ruminants (Osweiler, 2000). Deoxynivalenol levels in feeds have been correlated with reduced milk production (as reported in Jouany and Diaz, 2005); however, a cause and effect relationship was not established. Dairy cattle may be more sensitive to the effects of deoxynivalenol compared to beef cattle and sheep; an observation that could be due to higher level of stress to which dairy cattle are exposed (Jouany and Diaz, 2005). Compared to pigs, poultry are more resistant to deoxynivalenol but they are more sensitive than pigs to the toxic effects of T-2 toxin and diacetoxyscirpenol. T-2 toxin toxicosis has been reported to cause reduced egg production, increased incidence of cracked eggs and oral lesions (as reported in Devegowda and Murthy, 2005). Experimentally, horses are resistant to deoxynivalenol's effects on body weight gain (JECFA 56th, 2002). However, there is one report suggesting that deoxynivalenol exposure via contaminated bedding straw was the cause of sudden weight loss in stabled horses (as reported in Newman and Raymond, 2005). Shrimp, dogs and cats are sensitive to the emetic effects of deoxynivalenol (JECFA 56th, 2002).

5. Fumonisins

Field outbreaks of mouldy maize-induced equine leukoencephalomalacia (ELEM) have been reported since 1891 (Haliburton and Buck, 1986). Areas where ELEM has been reported include South America, China, Greece, France, New Caledonia, Egypt, South Africa, and Germany (Haliburton and Buck, 1986; Magnol et al., 1983; Laurent et al., 1998). In 1971 Wilson and Maronpot (1971) identified *F. verticillioides* as the predominant contaminant of mouldy maize that had caused cases of ELEM in Egypt and reproduced ELEM by feeding culture material of the fungus on maize. In 1981 *F. verticillioides* maize culture material was shown to induce porcine pulmonary edema (PPE) (Kriek et al., 1981), a disease that has been known in Hungary since 1950 (Fazekas et al., 1998). In 1988, shortly after the isolation and structure elucidation of fumonisins, Marasas et al. (1988) successfully produced ELEM in a horse. The following year there were numerous outbreaks of ELEM and PPE in the USA. PPE has been reproduced with pure fumonisin B_1 but only by intravenous injection (Harrison et al., 1990). While field outbreaks of PPE have not occurred in the USA since the early 1990s, reports of ELEM have persisted. Field outbreaks in poultry have been reported but the effects usually involve reduced performance and not mortality (WHO, 2000).

ELEM syndrome is a fatal disease that apparently occurs only in horses and related species and is characterized by the presence of liquefactive necrotic lesions in the white matter of the cerebrum, however, the gray matter may also be involved (WHO, 2000). Increased protein in the cerebrospinal fluid and other changes suggest that the cause of the brain lesion is vasogenic cerebral edema (Haschek et al., 2002). The first symptoms are lethargy, head pressing and decreased feed intake, followed by convulsions and death after several days. Early clinical signs include mild proprioceptive dysfunction such as hindlimb ataxia, delayed forelimb placing reactions and tongue paresis (Foreman et al., 2004). Ele-

vated serum enzyme levels indicative of liver damage are preceded by elevation in free sphingoid bases in serum. The serum enzymes often return to near normal concentrations but usually increase markedly immediately prior to or at the onset of behavioral changes (JECFA 56th, 2001; WHO, 2000). The elevation in free sphingoid bases occurs because fumonisins are inhibitors of the enzyme ceramide synthase. The elevation in serum and tissue of free sphingoid bases is a biomarker for exposure to toxic levels of fumonisins (Riley et al., 1994) and has been used in studies in horses, pigs, rabbits, poultry and other farm animals (WHO, 2000).

In addition to the brain lesions, histopathological abnormalities in liver and kidney have been reported in horses. Fatal liver disease in the absence of any brain lesions and ELEM concurrent with significant liver disease has been observed in horses and ponies. The length of exposure, level of contamination, individual animal differences, previous exposure, or pre-existing liver impairment may all contribute to the appearance of the clinical disease.

The minimum toxic dose in equids appears to be between 15 and 22 mg/kg feed, however, analysis of feeds from confirmed cases of ELEM indicated that consumption of feed with a fumonisin B_1 concentration greater than 10 mg/kg diet is associated with increased risk of development of ELEM, whereas, a concentration less than 6 mg/kg diet is not (JECFA 56th, 2001; WHO, 2000).

In pigs, clinical signs indicative of PPE syndrome typically occur soon (2–7 days) after consumption of diets containing large amounts of fumonisins over a short period of time. Clinical signs usually include decreased feed consumption, dyspnoea, weakness, cyanosis and death. At necropsy, the animals exhibit varying degrees of interstitial and interlobular oedema, with pulmonary oedema and hydrothorax**.** Varying amounts of clear yellow fluid accumulate in the pleural cavity. Toxic hepatosis occurs concurrently with PPE and is also observed in animals that consume high levels of fumonisins but do not develop PPE. There is a strong correlation between fumonisin content of maize screenings obtained from different farms and outbreaks of PPE. The minimum toxic dose has not been clearly established. Concentrations of fumonisin B_1 as low as 17 mg/kg in culture material diets induced PPE in 5 days, however, a dose of 150–170 mg/kg diet for up to 210 days caused liver effects early on but no evidence of pulmonary oedema (WHO, 2000). Tissues other than liver and lung have been reported to be targets for fumonisins (*e.g.*, pancreas, heart, kidney, pulmonary intravascular macrophages, and oesophagus). Altered growth and changes in selected haematological parameters in pigs were reported at dietary levels as low as 1 mg/kg (WHO, 2000); however, these studies have yet to be repeated.

Several reports have been published showing that feed contaminated with *F. verticillioides,* and by inference containing fumonisin, are the cause of poultry disease. The clinical features of the disease often include diarrhoea, weight loss, increased liver weight and poor performance. Functional and morphological changes were observed in chickens exposed to fumonisin B_1. Several studies have confirmed that culture materials or extracts of culture materials of *F. verticillioides* or *F. proliferatum* containing fumonisin B_1 and moniliformin are toxic to poultry (broiler chicks, turkeys, ducklings). The levels of fumonisins used in these studies were 75–644 mg/kg diet. Toxicity and altered haematological parameters have been documented in broiler chicks fed diets containing pure fumonisin B_1 (10 mg/kg) and fumonisin B_1 (30 mg/kg) from *F. verticillioides* culture material (JECFA 56th, 2001; WHO, 2000).

Other farm animals that have been studied using pure fumonisins, contaminated maize screenings or maize culture material of *F. verticillioides* include catfish, trout, cattle, mink, and rabbits. Rabbits are especially sensitive to renal toxicity. In all cases where toxicity was evident it involved liver and/or kidney or homologous organs and there was evidence of disruption of sphingolipid metabolism.

The elevation of free sphingoid bases in serum and urine has been proposed as a functional biomarker for exposure to fumonisins. This biomarker works well in farm animals (for example, Piva et al., 2005). Because fumonisins inhibit sphingolipid biosynthesis, it is likely that receptors and processes that are dependent on sphingolipids could be affected. For example, glycosphingolipids are necessary for the proper function of many membrane receptors including those for some vitamins (*i.e.* folate) and recognition of numerous microbial pathogens and microbial toxins (*i.e.* Shiga-like toxins and cholera toxin; Merrill et al., 2001). Studies have shown that fumonisin-treated pigs have increased susceptibility to intestinal infection with *E. coli* (Oswald et al., 2003) and decreased specific antibody response during vaccination (Taranu et al., 2005). Fumonisins frequently co-occur with aflatoxins in corn and have been shown to promote aflatoxin carcinogenicity in trout (IARC, 2002). Fumonisins also cause liver toxicity in catfish, poultry, mink, goats and cattle and promote aflatoxin-initiated liver tumors in rainbow trout (JECFA 56th, 2001). The relative sensitivity based on the USFDA Guidance to Industry (USFDA, 2001) is equids and rabbits > pigs and catfish > ruminants, poultry and mink.

6. Zearalenone

Zearalenone has been implicated in field outbreaks of reproductive problems, vulvovaginitis and anestrus in pigs (Raisbeck et al., 1991). The first report implicating the consumption of moldy feed with estrogenism in pigs was in 1928 (McNutt et al., 1928). In early work, zearalenone was called F-2 toxin (Mirocha et al., 1968). Field outbreaks of estrogenic syndrome in pigs have been reported in North America, Europe, Africa, Asia and Australia (Christensen, 1979). Reports of zearalenone-induced abortions in pigs are probably a result of implantation failure (Osweiler, 1986). Zearalenone is also suspected of causing reproductive problems in ruminants but this is considered controversial (Raisbeck et al., 1991). Zeranol, a semisynthetic zearalenone analog, is used in cattle as a growth promoter and the estrogenic effects caused reduced performance in bulls (Raisbeck et al., 1991). Sheep grazing grasses contaminated with zearalenone have been reported to have reproductive problems (CAST, 2003). Zearalenone was found to interfere in the induction of parturition by oxytocin in gilts and sows (Alexopoulos, 2001).

The primary effect of zearalenone is estrogenic and prepubertal female pigs are clearly the most affected farm animals. The basis for the estrogenic effect is well established and is due to a close structural similarity between zearalenone (and many of its metabolites) and estradiol (Osweiler, 2000). Alpha zearalenol is three times more potent in its estrogenic activity compared to zearalenone and the relative binding affinity for estrogen receptors was greater in pig than in other species; which may explain the interspecies differences in sensitivity to the estrogenic effects (Fitzpatrick et al., 1989). Clinical signs of estrus can be induced in ovariectomized sows and doses as low as 1–5 mg/kg can induce vulvovaginitus,

tenesmus, vaginal and rectal prolapse in young female pigs (Osweiler, 1986). Effects on prepubertal boars have also been reported and include reduced libido, plasma testosterone and other effects (Osweiler, 1986). Dietary levels of 3–10 mg/kg zearalenone can induce anestrus in sows, reduced litter size, fetal resorption and implantation failure. Cattle are more resistant to the estrogenic effects; however, conception rates can be reduced in females (Weaver et al., 1986) while testicular atrophy was reported in bulls (Danicke et al., 2002). Poultry are considered to be resistant (Haschek et al., 2002). Cycling mares also appear to be relatively insensitive to the estrogenic effects of zearalenone at low doses (equivalent to natural contamination) (Juhasz et al., 2001).

7. Other *Fusarium* mycotoxin

Other *Fusarium* mycotoxins that are sometimes found in animal feeds include HT-2 toxin, moniliformin, fusarochromanone, and fusaric acid. In the last few years, the approach of investigating the toxicity of *Fusarium* strains isolated from feeds (but not necessarily associated with overt animal health and production symptoms) has lead to the discovery of new mycotoxins such as sambutoxin (Kim and Lee, 1994), apicidin (Park et al., 1999), and 2-amino-14,16-dimethyloctadecan-3-ol, a sphingosine competitor similar to fumonisins (Uhlig et al., 2005). Proven farm animal disease outbreaks that are due to consumption of feeds contaminated with these mycotoxins are not readily available; however, it is likely that their co-occurrence with other more common *Fusarium* mycotoxins could contribute to field outbreaks.

8. Conclusions

While mouldy feeds were known to be the cause of farm animal diseases for many years, the mycotoxins responsible for the diseases were not identified until much later. Today, there is considerable evidence for the potential of mycotoxins in mouldy feedstuffs to cause animal disease. *Fusarium* fungi are widespread in feedstuffs and are known causes of animal disease. The most common *Fusarium* toxins in feedstuffs are deoxynivalenol, fumonisin and zearalenone. It is highly likely that many other *Fusarium* mycotoxins remain to be discovered and like those that have been discovered in the past, the first indication that a mycotoxin might be involved will be a close association between consumption of mouldy feed and the onset of altered performance or behavior. Identifying the fungus and reproducing the disease using culture material will be the crucial first step in identifying the responsible toxin. No doubt, an unexplained field disease outbreak is an event to be avoided. However, it is also an opportunity for gaining valuable insight into understanding the underlying cause of disease processes and thus is not a cloud without its silver lining.

References

Abramson, D., Mills, J.T., Marquardt, R.R., Frohlich, A.A., 1997. Mycotoxins in fungal contaminated samples of animal feed from western Canada, 1982–1994. Can. J. Vet. Res. 61, 49–52.

Alexopoulos, C., 2001. Association of *Fusarium* mycotoxicosis with failure in applying an induction of parturition program with PGF2alpha and oxytocin in sows. Theriogenology 55, 1745–1757.

Binder, E.M., Tan, L.M., Chin, L.J., Handl, J., Richard, J., 2007. Worldwide occurrence of mycotoxins in commodities, animal feed and feed ingredients. In: D.P. Morgavi, R.T. Riley (Eds.), *Fusarium* and their toxins: Mycology, occurrence, toxicity, control and economic impact. Anim. Feed Sci. Technol.

Bohm, J., Razzazi-Fazeli, E., 2005. Effects of mycotoxins on domestic pet species. In: Diaz, D.E. (Ed.), The Mycotoxin Blue Book. Nottingham University Press, Nottingham, UK, pp. 77–91.

Bondy, G.S., Pestka, J.J., 2000. Immunomodulation by fungal toxins. J. Toxicol. Environ. Health, Part B 3, 109–143.

Butler, W.H., 1974. In: Purchase, I.F.H. (Ed.), Aflatoxins. Mycotoxins Elsevier Scientific Publishing Co., New York, pp. 1–28.

CAST, 2003. Mycotoxins: Risks in Plant and Animal Systems, Task Force Report 138. Council for Agricultural Science and Technology, Ames, Iowa.

Christensen, C.M., 1979. Zearalenone. In: Shimoda, W. (Ed.), Conference on Mycotoxins in Animal Feeds and Grains Related to Animal Health. US Department of Commerce, National Technical Information Service, Springfield, VA, pp. 1–79.

Christensen, C.M., 1980. Ergots. In: Shimoda, W. (Ed.), Conference on Mycotoxins in Animal Feeds and Grains Related to Animal Health. US Dept. of Commerce, National Technical Information Service, Springfield, VA, pp. 1–44.

Cousin, M.A., Riley, R.T., Pestka, J.J., 2005. Foodborne mycotoxins: chemistry, biology, ecology, and toxicology. In: Fratamico, P.M., Bhunia, A.K. (Eds.), Foodborne Pathogens: Microbiology and Molecular Biology. Horizon Scientific Press, Ltd., Norfolk, UK, pp. 163–226.

Danicke, S., Gadeken, D., Ueberschar, K.H., Meyer, U., Scholz, H., 2002. Effects of *Fusarium* toxin contaminated wheat and of a detoxifying agent on performance of growing bulls, on nutrient digestibility in wethers and on the carry over of zearalenone. Arch. Tierernahr. 56, 245–261.

Devegowda, G., Murthy, T.N.K., 2005. Mycotoxins: their effects in poultry and some practical solutions. In: Diaz, D.E. (Ed.), The Mycotoxin Blue Book. Nottingham University Press, Nottingham, UK, pp. 25–56.

Diaz, D.E. (Ed.), 2005. The Mycotoxin Blue Book. Nottingham University Press, Nottingham, UK.

Fazekas, B., Bajmocy, E., Glavits, R., Fenyvesi, A., Tanyi, J., 1998. Fumonisin B1 contamination of maize and experimental acute fumonisin toxicosis in pigs. J. Vet. Med. B Infect. Dis. Vet. Public Health 45, 171–181.

Fink-Gremmels, J., Malekinejad, H., 2007. Biochemical mechanisms and clinical effects associated with exposure to the mycoestrogen zearalenone. In: Morgavi, D.P., Riley, R.T. (Eds.), *Fusarium* and their toxins: Mycology, occurrence, toxicity, control and economic impact. Anim. Feed Sci. Technol.

Fitzpatrick, D.W., Picken, C.A., Murphy, L.C., Buhr, M.M., 1989. Measurement of the relative binding affinity of zearalenone, alpha-zearalenol and beta zearalenol for uterine and oviduct estrogen receptors in swine, rats and chickens: an indicator of estrogenic potencies. Comp. Biochem. Physiol. C 94, 691–694.

Foreman, J.H., Constable, P.D., Waggoner, A.L., Levy, M., Eppley, R.M., Smith, G.W., Tumbleson, M.E., Haschek, W.M., 2004. Neurological abnormalities and cerebrospinal fluid changes in horses administered fumonisin B1 intravenously. J. Vet. Int. Med. 18, 223–230.

Forgacs, J., Carll, W.T., 1962. Mycotoxicoses. In: Brandly, C.A., Jungherr, E.L. (Eds.), Advances in Veterinary Sciences. Academic Press, New York, pp. 274–382.

Haliburton, J.C., Buck, W.B., 1986. Equine leucoencephalomalacia: an historical review. In: Richard, J.L., Thurston, J.R. (Eds.), Diagnosis of Mycotoxicoses. Martinus Nijhoff Publishers, Dordrecht, pp. 75–80.

Hamilton, P.B., 1982. Mycotoxins and farm animals. Refush Vet. 39, 17–45.

Hamilton, P.B., Huff, W.E., Harris, J.R., 1977. Field episodes of ochratoxicosis in poultry. Poult. Sci. 56, 1719.

Harrison, L.R., Colvin, B.M., Greene, J.T., Newman, L.E., Cole Jr., J.R., 1990. Pulmonary edema and hydrothorax in swine produced by fumonisin B_1, a toxic metabolite of *Fusarium moniliforme*. J. Vet. Diagn. Invest. 2, 217–221.

Haschek, W.M., Voss, K.A., Beasley, V.R., 2002. Selected mycotoxins affecting animal and human health. In: Haschek, W.M., Rousseaux, C.G., Wallig, M.A. (Eds.), Handbook of Toxicologic Pathology, 1, 2nd ed. Academic Press, New York, pp. 645–699.

Hesseltine, C.W., 1979. Introduction, definition and history of mycotoxins of importance to animal production. In: Interactions of Mycotoxins in Animal Production. National Academy of Sciences, Washington, pp. 3–18.

IARC, 2002. Fumonisin B_1. In: Some Traditional Herbal Medicines, Some Mycotoxins, Naphthalene and Styrene. Lyon, International Agency for Research on Cancer, pp. 275–366 (IARC Monographs on the Evaluation of Carcinogenic Risk to Humans, vol. 82).

JECFA 56th. 2001. Safety Evaluation of Certain Mycotoxins in Food. WHO Food additives Series, No. 47, Geneva, Switzerland.

Jouany, J.-P., Diaz, D.E., 2005. Effects of mycotoxins in ruminants. In: Diaz, D.E. (Ed.), The Mycotoxin Blue Book. Nottingham University Press, Nottingham, UK, pp. 295–321.

Juhasz, J., Nagy, P., Kulcsar, M., Szigeti, M., Reiczigel, J., Huszenicza, G., 2001. Effect of low-dose zearalenone exposure on luteal function, follicular activity and uterine oedema in cycling mares. Acta Vet. Hung. 49, 211–222.

Kim, J.C., Lee, Y.W., 1994. Sambutoxin, a new mycotoxin produced by toxic *Fusarium* isolates obtained from rotted potato tubers. Appl. Environ. Microbiol. 60, 4380–4386.

Kriek, N.P.J., Kellerman, T.S., Marasas, W.F.O., 1981. A comparative study of the toxicity of *Fusarium verticillioides* (= *F. moniliforme*) to horses, primates, pigs, sheep and rats. Onderstepoort J. Vet. Res. 48, 129–131.

Krogh, P., 1978. Mycotoxic nephropathy. In: Wyllie, T.D., Morehouse, L.G. (Eds.), Mycotoxic Fungi, Mycotoxins, Mycotoxicoses, vol. 2. Marcel Dekker, Inc., New York, pp. 236–255.

Laurent, D., Costa, R., Modesto, J., Kohler, F., Le Bars, P., Pellegrin, F., 1998. Fumonisin: a major problem in New-Caledonia. Rev. Med. Vet. (Toulouse) 149, 702.

Magnol, J.P., Le Bars, J., Quere J.-P., 1983. Leucoencephalomalacie toxique chez le cheval. Rev. Med. Vet. (Toulouse) 134, 297–299.

Marasas, W.F., Kellerman, T.S., Gelderblom, W.C., Coetzer, J.A., Thiel, P.G., van der Lugt, J.J., 1988. Leukoencephalomalacia in a horse induced by fumonisin B1 isolated from *Fusarium moniliforme*. Onderstepoort J. Vet. Res. 55, 197–203.

McNutt, S.H., Purwin, P., Murray, C., 1928. Vulvovaginitis in swine. J. Am. Vet. Med. Assoc. 73, 484–492.

Meky, F.A., Turner, P.C., Ashcroft, A.E., Miller, J.D., Qiao, Y.-L., Roth, M.J., Wild, C.P., 2003. Development of a urinary biomarker of human exposure to deoxynivalenol. Food Chem. Toxicol. 41, 265–273.

Merrill Jr., A.H., Sullards, M.C., Wang, E., Voss, K.A., Riley, R.T., 2001. Sphingolipid metabolism: roles in signal transduction and disruption by fumonisins. Environ. Health Perspect. 109, 283–289.

Mirocha, C.J., Christensen, C.M., Nelson, G.H., 1968. Physiologic activity of some fungal estrogens produced by *Fusarium*. Cancer Res. 28, 2319–2322.

Moorooka, N., Uratsuji, N., Yoshizawa, T., Yamamoto, H., 1972. Studies on the toxic substances in barley infected with *Fusarium* spp. J. Food Hyg. Soc. Jpn. 13, 368–375.

National Academy of Sciences, 1979. Interactions of mycotoxins in animal production. National Academy of Sciences, Washington.

Newman, K.E., Raymond, S.L., 2005. Effects of mycotoxins in horses. In: Diaz, D.E. (Ed.), The Mycotoxin Blue Book. Nottingham University Press, Nottingham, UK, pp. 57–76.

Oswald, I.P., Desautels, C., Lafitte, J., Fournout, S., Peres, S.Y., Odin, M., LeBars, P., LeBars, J., Fairbrother, J.M., 2003. The mycotoxin fumonisin B_1 increases intestinal colonization by pathogenic *Escherichia coli* in pigs. Appl. Environ. Microbiol. 69, 5870–5874.

Osweiler, G.D., 1986. Occurrence and clinical manifestations of trichothecene toxicoses and zearalenone toxicoses. In: Richard, J.L., Thurston, J.R. (Eds.), Diagnosis of Mycotoxicoses. Martinus Nijhoff Publishers, Dordrecht, pp. 31–42.

Osweiler, G.D., 2000. Mycotoxins—contemporary issues of food animal health and productivity. Vet. Clin. North Am. Food Anim. Pract. 16, 511–530.

Park, J.S., Lee, K.R., Kim, J.C., Lim, S.H., Seo, J.A., Lee, Y.W., 1999. A hemorrhagic factor (Apicidin) produced by toxic *Fusarium* isolates from soybean seeds. Appl. Environ. Microbiol. 65, 126–130.

Pestka, J.J., 2007. Deoxynivalenol: toxicity, mechanisms and health risks. In: Morgavi, D.P., Riley, R.T. (Eds.), *Fusarium* and their toxins: Mycology, occurrence, toxicity, control and economic impact. Anim. Feed Sci. Technol.

Piva, A., Casadei, G., Pagliuca, G., Cabassi, E., Galvano, F., Solfrizzo, M., Riley, R.T., Diaz, D.E., 2005. Inability of activated carbon to prevent the toxicity of culture material containing fumonisin B1 when fed to weaned piglets. J. Anim. Sci. 83, 1939–1947.

Placinta, C.M., D'Mello, J.P.F., Macdonald, A.M.C., 1999. A review of worldwide contamination of cereal grains and animal feed with *Fusarium* mycotoxins. Anim. Feed Sci. Technol. 78, 21–37.

Raisbeck, M.F., Rottinghaus, G.E., Kendall, J.D., 1991. Effects of naturally occurring mycotoxins on ruminants. In: Smith, J.E., Henderson, R.S. (Eds.), Mycotoxins and Animal Foods. CRC Press, Boca Raton, pp. 647–677.

Richard, J.L., Thurston, J.R. (Eds.), 1986. Diagnosis of Mycotoxicoses. Martinus Nijhoff Publishers, Dordrecht.

Riley, R.T., Wang, E., Merrill Jr., A.H., 1994. Liquid chromatography of sphinganine and sphingosine: use of the sphinganine to sphingosine ratio as a biomarker for consumption of fumonisins. J. AOAC Int. 77, 533–540.

Rotter, B.A., Prelusky, D.B., Pestka, J.J., 1996. Toxicology of deoxynivalenol (vomitoxin). J. Toxicol. Environ. Health 48, 101–134.

Shreeve, B.J., Patterson, D.S., Roberts, B.A., 1975. Investigation of suspected cases of mycotoxicosis in farm animals in Britain. Vet. Rec. 97, 275–278.

Taranu, I., Marin, D.E., Bouhet, S., Pascale, F., Bailly, J.D., Miller, J.D., Pinton, P., Oswald, I.P., 2005. Mycotoxin fumonisin B1 alters the cytokine profile and decreases the vaccinal antibody titer in pigs. Toxicol. Sci. 84, 301–307.

Trenholm, H.L., Prelusky, D.B., Young, J.C., Miller, J.D., 1988. Reducing mycotoxins in animal feeds. Agriculture Canada Publication 1827E. Communications Branch, Agriculture Canada, Ottawa.

Uhlig, S., Petersen, D., Flåøyen, A., Wilkins, A., 2005. 2-Amino-14,16-dimethyloctadecan-3-ol, a new sphingosine analogue toxin in the fungal genus *Fusarium*. Toxicon 46, 513–522.

USFDA, 2001. (U.S. Food and Drug Administration Center for Food Safety and Applied Nutrition, Center for Veterinary Medicine) Background paper in support of fumonisin levels in animal feed: executive summary of this scientific support document. (http://www.cfsan.fda.gov/~dms/fumonbg4.html).

Vesonder, R.F., Ciegler, A., Jensen, A.H., 1973. Isolation of the emetic principle from *Fusarium*-infected corn. Appl. Microbiol. 26, 1008–1010.

Voss, K.A., Smith, G.W., Haschek, W.M., 2007. Fumonisins: toxicokinetics, mechanism of action and toxicity. In: Morgavi, D.P., Riley, R.T. (Eds.), *Fusarium* and their toxins: Mycology, occurrence, toxicity, control and economic impact. Anim. Feed Sci. Technol.

Weaver, G.A., Kurtz, H.J., Behrens, J.C., Robison, T.S., Seguin, B.E., Bates, F.Y., Mirocha, C.J., 1986. Effect of zearalenone on the fertility of virgin dairy heifers. Am. J. Vet. Res. 47, 1395–1397.

Whitaker, T.B., Slate, A.B., Johansson, A.S., 2005. Sampling feeds for mycotoxin analysis. In: Diaz, D.E. (Ed.), The Mycotoxin Blue Book. Nottingham University Press, Nottingham, UK, pp. 1–23.

Wilson, B.J., Maronpot, R.R., 1971. Causative fungus agent of leukoencephalomalacia in equine animals. Vet. Rec. 88, 484–486.

WHO – Environmental Health Criteria, 219: Fumonisin B_1, 2000. In: Marasas, W.H.O., Miller, J.D., Riley, R.T., Visconti, A. (Eds.), International Programme on Chemical Safety, United Nations Environmental Programme, The International Labour Organization, and the World Health Organization, Geneva, Switzerland.